CHAPTER 4

Anemia

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Anemia is a type of red blood cell disorder that has a multitude of etiologies as well as varying degrees of severity ranging from completely asymptomatic anemia to the most severe form, which can cause death in utero. It is defined by low total body RBC mass that leads to a low hemoglobin and low hematocrit. The normal hemoglobin and hematocrit vary from individual to individual depending on age, sex, menstruation status, race, altitude, and exposure to tobacco smoke. Conditions that decrease oxygen delivery to cells, at any level, may necessitate an increase in RBC mass to compensate because hemoglobin is the sole oxygen transporter for the body. Table 4-1 gives the normal hemoglobin and hematocrit levels for different populations.

The change in hemoglobin levels as children age can be attributed to changes in erythropoietin levels. A normal physiologic period of anemia is expected in all infants at 1 to 2 months. This anemia begins to resolve at about 1 to 2 years of age.

Anemias can be categorized by two main classification systems: morphologic and pathophysiologic. The pathophysiologic system of anemia classification is less commonly used, but is just as easy to understand. This system broadly separates anemias by the *cause* of low red blood cell (RBC) mass into two categories: increased destruction versus decreased production. The more commonly used classification system, however, is the morphologic system that categorizes anemias based on the size of the red cells. In order to understand this classification system it is important to remember what the various lab values within the complete blood cell (CBC) count mean. Table 4-2 defines these values.

The morphologic classification system uses the mean corpuscular volume (MCV) to categorize anemias into three major types: macrocytic, normocytic, and microcytic. Normocytic anemia is defined by an MCV of 80 to 100 fL. Macrocytic anemia includes anemias with an MCV of more than 100 fL, whereas microcytic anemia includes those with an MCV less than 80 fL. The other two values mentioned in Table 4-3 (in macrocytic anemia; megaloblastic vs nonmegaloblastic; in normocytic anemia; hemolytic vs nonhemolytic) can be used to further identify the type of anemia once the general category is determined. In this chapter we address each general morphologic category of anemia separately. Table 4-3 lists the types of anemia by morphologic categorization.

Table 4-1. Normal Laboratory Values

AGE	HEMOGLOBIN	HEMATOCRIT
Men and nonmenstruating women	13-14 g/dL	41%
Menstruating women	12 g/dL	37%
Infants at birth	16.5 g/dL	50%
First week of life	18.5 g/dL	56%
Age 1-2 months	11.5 g/dL	36%
Adolescent boy	15 g/dL	47%
Adolescent girl	14 g/dL	47%

Table 4-2. Understanding the Complete Blood Count

Hematocrit	Percent of total blood occupied by red blood cells (RBCs)
MCV	Average size of RBC; used to classify anemias; normal is 80 to 100 fL
MCHC	Amount of hemoglobin per RBC; normal is 32 to 36 g/dL
RDW	Variation in size among RBCs; normal is 12% to 15%

MCV, mean corpuscular volume; *MCHC,* mean corpuscular hemoglobin; *RDW,* red cell distribution width.

The screening recommendations per the US Preventive Services Task Force (USPSTF) are as follows: (1) all pregnant women at their first prenatal visit and all nonpregnant women beginning in adolescence and then every 5 to 10 years until menopause; and (2) screen high-risk infants with a single hemoglobin and hematocrit between 6 and 12 months of age.

MACROCYTIC ANEMIA

Macrocytic anemia is defined by an MCV of greater than 100 fL. It is further divided into megaloblastic or nonmegaloblastic. Megaloblasts are large, immature, nucleated RBCs. Megaloblastic anemia is caused by impaired deoxyribonucleic acid (DNA) synthesis, which causes dyssynchrony of cell replication and division. It is usually due to a deficiency of either cobalamin (vitamin B_{12}) or folic acid. Severe macrocytic anemia (MCV >125 fL) is almost always

Table 4-3. Morphologic Anemia Classification

MACROCYTIC (MCV >100 fL)	NORMOCYTIC (MCV 80–100 fL)	MICROCYTIC (MCV <80 fL)
MEGALOBLASTIC	HEMOLYTIC (2 subclasses)	Iron deficiency
B_{12} deficiency	(1) RBC INTRINSIC	Thalassemias
Folate deficiency	Membranopathy (i.e., HS)	Sideroblastic
Drug related, (i.e., hydroxyurea)	Hemoglobinopathy (i.e., SCD)	Anemia of chronic disease
NONMEGALOBLASTIC	Enzymopathy (i.e., G6PD deficiency)	Lead poisoning
Hypothyroidism	(2) RBC EXTRINSIC	Hodgkin's lymphoma
Liver disease	Autoimmune mediated (SLE, drug, virus, lymphoid disorder, idiopathic)	Castleman's disease
Alcoholism	Alloimmune mediated (transfusion reaction, neonatal hemolysis)	
Myelodysplasia	Microangiopathic (i.e., TTP/HUS)	
Reticulocytosis (hemolysis, bleeding)	Infection (i.e., malaria)	
	Chemical agents (i.e., venoms)	
	Splenomegaly	
	NONHEMOLYTIC	
	Acute blood loss	
	Anemia of chronic disease	
	Chronic renal insufficiency	
	Intrinsic bone marrow problem (aplastic anemia, PNH, pure red cell aplasia, etc.)	
	Extrinsic bone marrow problem (drugs, toxins, radiation, endocrine, infiltrative cancer, immune mediated, etc.)	

G6PD, Glucose-6 phosphate dehydrogenase; *HS,* hereditary spherocytosis; *HUS,* hemolytic uremic syndrome; *MCV,* mean corpuscular volume; *PNH,* paroxysmal nocturnal hemoglobinuria; *RBC,* red blood cell; *SCD,* sickle cell disease; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

megaloblastic, with a few exceptions for the myelodysplastic syndromes. Nonmegaloblastic macrocytic anemias encompass the rest of the macrocytic anemias including drugs, alcoholism, hypothyroidism, myelodysplasia, and chronic liver disease. Vitamin B_{12} and folate deficiency are discussed in this section.

FOLIC ACID DEFICIENCY

Folic acid is tetrahydrofolate, which is needed for many reactions involving one-carbon transfers. Two of the important reactions it is required for are shown in the following text. The products are important in DNA synthesis.

Symptoms

- Fatigue
- Anorexia ++
- Weight loss
- Diarrhea ++
- Lightheadedness
- Abdominal pain

Signs

- Pallor
- Glossitis
- Jaundice
- Absent neurologic symptoms

Workup

History is the initial step in workup. Folate is found in most fruits and vegetables and daily requirements (50 to 100 mcg/day) are usually met with diet. The body stores only 2 to 3 months of folic acid, so dietary deficiency is more common than with B_{12}. At-risk patients include alcoholics, anorexic patients, older adult patients, those who avoid fruits and vegetables, and those who overcook their food, because the vitamin is labile.

- Unlike B_{12} deficiency, folate deficiency is less likely due to malabsorption because the entire GI tract absorbs folic acid. Occasionally, however, small intestine diseases such as gluten enteropathy, tropical sprue, and Crohn's disease can be a factor, so comorbid conditions should always be considered. Drugs such as trimethoprim, phenytoin, oral contraceptives, and sulfasalazine may interfere with absorption.
- During times of growth, such as pregnancy, the folic acid requirement is 5 to 10 times greater than normal. Other causes of increased demand include exfoliative skin disease, chronic hemolytic anemia, and dialysis.
- Laboratory workup reveals an anemia with an MCV more than 100 fL and normal B_{12} levels. The peripheral blood smear will look identical to one found in B_{12} deficiency. Serum homocysteine

levels will also be elevated in folate deficiency. An RBC folate level of less than 150 ng/mL is diagnostic and is a more precise indicator of chronic folate deficiency. Total serum folate is also reduced but this is influenced more by recent dietary intake.

Comments and Treatment Considerations

Treatment is with replacement of folic acid, 1 mg/day orally. This is also the recommended dose for pregnant patients. In cases of malabsorption, doses of up to 5 mg/day may be required. Parenteral folate is rarely necessary. Foods rich in folate should be encouraged. These include leafy green vegetables, citrus fruits, nuts, beans, wheat germ, and liver. There is rapid improvement as seen with B_{12} supplementation. There is an immediate sense of well-being, and reticulocytosis occurs within 5 to 7 days. Within 2 months one can expect a total correction of the anemia. Treating folic acid deficiency can allow underlying neurologic damage from B_{12} deficiency to progress, so it is important to rule out a coexisting condition.

VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} is a member of the cobalamin family and is essential for important enzymatic reactions in DNA synthesis. B_{12} is also required for the body to hold on to its folic acid stores. Therefore, if a patient is B_{12} deficient, he or she will likely also become folate deficient. Lack of B_{12} can lead to abnormal myelin synthesis due to inefficient methionine production. Meat contains B_{12} and an acidic stomach is necessary for the vitamin to be freed. After B_{12} is ingested it is bound to intrinsic factor (IF) in the stomach and transported to the terminal ileum, where it is absorbed. Gastric parietal cells secrete IF.

Symptoms

- Fatigue
- Weight loss
- Anorexia ++
- Diarrhea ++
- Lightheadedness
- Abdominal pain
- Peripheral paresthesias, then balance disturbance
- If severe, cerebral function may be affected, as well as vision, taste, smell
- Rarely dementia and neuropsychiatric changes precede hematologic changes.

Signs

- Glossitis
- Pallor
- Jaundice
- Decreased vibration and position sense
- Weakness
- Reflexes may be diminished or increased.

Workup

- The history is a key part of the workup. Specific attention should be given to diet. All animal products contain B_{12}, so rarely is dietary intake to blame for deficiency. Additionally, the liver stores 2 to 3 years' worth of B_{12}. Complete vegetarians, however, are at risk.
- More often, the cause of B_{12} deficiency is due to a defect in absorption and transport. The most common cause is pernicious anemia, which is caused by the absence of IF due to atrophy of the gastric mucosa or autoimmune destruction of the gastric parietal cells. It occurs most often in people around age 60, although a form of juvenile pernicious anemia is known. The incidence of pernicious anemia is increased in patients with other autoimmune diseases. Laboratory examination may reveal antiparietal cell antibodies (90%) or anti-IF antibodies (60%). The most characteristic finding is gastric atrophy sparing the antrum. Hypergastrinemia is also characteristic.
- Surgical history is also important. Total gastrectomy removes the source of IF. Partial gastrectomy may also be a cause although the exact mechanism is unclear. Ileal resection is another inciting factor.
- Ingestion of corrosive agents that damage the gastric mucosa can also remove IF.
- Many drugs can interfere with many levels of red cell production.
- Drugs that decrease gastric acid production can interfere with the release of B_{12} from food. Patients older than age 70 commonly have low gastric acid levels so are unable to absorb B_{12} from food. They are able to absorb the B_{12} found in vitamins, however.
- Chronic diarrhea can indicate malabsorption such as tropical sprue. Chronic constipation can indicate intestinal stasis due to strictures, diverticula, diabetes mellitus, scleroderma, or amyloidosis, which results in stasis in the bowel and an overgrowth of bacteria that degrade B_{12} before it can be absorbed.
- More rare causes of B_{12} deficiency are fish tapeworm infection, pancreatic insufficiency, and severe Crohn's disease.
- Laboratory examination reveals an anemia with a MCV between 110 and 140 fL. It is possible to have B_{12} deficiency with a normal MCV, however. This is sometimes explained by a concomitant thalassemia or iron deficiency. If severe, the hematocrit may be as low as 10% to 15% and one may also see thrombocytopenia and/or leukopenia. Serum B_{12} levels are less than 170 pg/mL (170 to 240 is borderline) and there is an increase in methylmalonic acid (MMA) and homocysteine levels. The peripheral smear shows anisocytosis and poikilocytosis, but the characteristic finding is the macro-ovalocyte. Reticulocyte count is reduced and lactate dehydrogenase (LDH) is elevated.

Comments and Treatment Considerations

Intramuscular B_{12} injections are historically used to treat vitamin B_{12} deficiency anemia. Injections of 100 mcg are given daily for 1 week, then weekly for 1 month, then monthly for life. Oral B_{12} can also be used with similar results. The dose currently supported in the

literature is 2000 mcg/day. Patients respond with reticulocytosis within 5 to 7 days and feel a sense of wellness almost immediately. Hypokalemia and salt retention can occur during early therapy. CNS effects are generally irreversible unless they have ensued within the last 6 months. Folate supplementation may increase the likelihood of neurologic sequelae of B_{12} deficiency.

MICROCYTIC ANEMIA

Microcytic anemia is defined as a MCV less than 80 fL. Microcytic anemia may result from iron deficiency, thalassemia, anemia of chronic disease, lead toxicity, or sideroblastic anemia. Iron deficiency and thalassemia are two of the more common causes of microcytic anemia.

IRON DEFICIENCY

Iron is needed for hemoglobin synthesis among other things. If iron stores are inadequate, then anemia ensues.

Symptoms

- May be asymptomatic, especially in early stages +++
- Pallor
- Fatigue
- Orthostatic hypotension
- Exercise intolerance
- Palpitations

Signs

- Koilonychia (spoon nails)
- Atrophic glossitis
- Alopecia
- Esophageal web (Plummer-Vinson syndrome)
- Pica (a craving for nonfood items such as ice or clay)
- Tachycardia
- Blue sclera

Workup

- Perform CBC and MCV. If the MCV is less than 80 fL and the hemoglobin falls below the expected range, then the patient has microcytic anemia. The next step is to perform a serum iron panel including a ferritin, iron level, total iron-binding capacity (TIBC), and percent saturation. Refer to Table 4-4 for differential diagnosis based on laboratory results. If the diagnosis is still not clear, hemoglobin electrophoresis, peripheral blood smear, and lead levels should be obtained.
- Serum iron levels less than 60 μg/dL, ferritin levels less than 30 ng/dL, TIBC greater than 400 μg/dL, and percent transferring saturation less than 15% are indicative of iron deficiency. It is important to

Table 4-4. Iron Studies in the Evaluation of Anemia

STUDY	IRON DEFICIENCY	CHRONIC DISEASE	THALASSEMIA
Ferritin	Low	Normal or high	Normal or high
Iron	Low	Low or normal	Normal or high
TIBC	Normal or high	Normal	Normal
% Saturation	Low	Low or normal	Normal or high

TIBC, Total iron-binding capacity.

note that ferritin is an acute phase reactant and can be elevated during times of stress. On peripheral smear, iron deficient red cells appear small and hypochromic. They also demonstrate a high red-cell distribution width (RDW).

- An easy way to diagnose iron deficiency is to monitor response to treatment. This can be done by checking a reticulocyte count several days after initiating therapy.

Comments and Treatment Considerations

Iron deficiency is the most common cause of anemia, with 11% of women and 4% of men being deficient. Not all those that are deficient are anemic. Deficiency results from either excessive loss or poor intake. The most common cause of iron deficiency is chronic blood loss.

The first consideration in treating microcytic anemia caused by iron deficiency is to identify and treat the cause of the chronic blood loss. Causes may include excessive menstrual bleeding (the most common cause in young women; oral contraceptives can be useful). GI bleeding (upper GI bleeding is seen with ulcers, hiatal hernias, and varices; lower GI bleeding can be seen in Crohn's disease, celiac sprue, colon cancer, and parasitic infection), bladder cancer, prostate cancer, and urolithiasis (standard urinalysis is the first step in determining if blood is being lost in the urine). Factitious bleeding should be considered when other chronic blood loss workup is negative.

Iron supplementation is needed to replenish depleted iron stores. Oral iron is initially used as a replacement. Ferrous sulfate, ferrous gluconate, and ferrous fumarate are all oral formulations that can be used for replacement. Ferrous sulfate is the least expensive of the oral iron preparations. The 325-mg dose given three or four times daily is used for replacement. Ascorbic acid, 250 mg, can be given with the iron supplement to enhance the degree of iron absorption.

Ferrous fumarate contains 66 mg of elemental iron combined with 125 mg of ascorbic acid. The tablet is provided in 200 mg doses and is given three or four times daily. Iron should be given 2 hours before or 4 hours after ingestion of antacids, or they will not be absorbed optimally. Patients should be informed that oral iron supplements can cause constipation, so adequate water intake is essential and stool softeners may become necessary.

There are various reasons that oral formulations may not work for an individual. GI tract symptoms caused by excessive iron intake can ultimately decrease absorption or patients may simply not tolerate oral iron. Patients with chronic malabsorption or ongoing blood loss may not be able to take oral formulations. Tetracyclines, quinolones, cereals, tea, coffee, eggs, and milk can decrease the absorption of oral iron. Infection with *Helicobacter pylori* also impairs oral iron absorption. If *H. pylori* is suspected, serum *H. pylori* antibody or a urea breath test should be obtained to test for infection.

When oral iron preparations are not being tolerated or absorbed, IV and intramuscular (IM) formulations such as INFeD and DexFerrum can also be used for iron replacement. DexFerrum, 25 to 100 mg IM, can be given daily as needed. IV and IM preparations should only be used when oral preparations fail to increase serum hemoglobin. Parenteral administration of iron preparations carries a higher risk for anaphylaxis, phlebitis, fever, and muscle breakdown.

The duration of treatment is not well agreed on. Some physicians replace iron only until hemoglobin levels return to within normal limits. Other physicians replace iron 6 months after the return of a normal hemoglobin level. Some clinicians consider iron deficiency successfully treated when the serum ferritin level reaches 50 ng/mL.

A diet high in iron should be encouraged. These foods include meats such as liver and fish, whole grains, nuts, seeds, leafy green vegetables, and dried fruit.

THALASSEMIA

Thalassemia results from a genetic mutation in the genes that code for the proteins that make up the alpha and beta chains of hemoglobin. This condition results in defective hemoglobin production, thus fewer red cells.

Symptoms

- Depends on the type of thalassemia
- May be asymptomatic +++
- Pallor
- Fatigue
- Irritability
- Growth restriction
- Shortness of breath
- Headache
- Dizziness

Signs

- Thalassemias may have no clinical signs evident on physical examination. +++
- Most of the signs of β-thalassemia major first become evident as fetal hemoglobin begins to convert to adult hemoglobin at 6 months of age.

- Abdominal swelling (due to hepatosplenomegaly)
- Jaundice (secondary to hemolytic anemia)
- RUQ pain (cholelithiasis, bilirubin gallstones)
- Clinical signs of congestive heart failure, severe edema
- Signs of infection

Workup

- Thalassemias are more common among patients of Mediterranean, African, and South Asian ancestry. This is partly because thalassemia confers a survival advantage to these groups should they become infected with malaria.
- Taking a careful family history is the first step because this is a genetic disease.
- Laboratory workup is the cornerstone to diagnosing thalassemia. The CBC will show microcytic anemia with an MCV less than 80 fL. The CBC may show an elevated RBC count despite decreased hemoglobin. A key difference from iron deficiency anemia is that the RDW is normal. At this point iron studies are performed that will likely rule out iron deficiency unless there is a coexisting condition. The next step therefore is hemoglobin electrophoresis. Abnormal electrophoresis results indicate thalassemia as the etiology of the microcytic anemia and differentiate the type.

Comments and Treatment Considerations

Adult hemoglobin, hemoglobin A, consists of two α- and two β-globin chains. Thalassemias result when defects are present in the production of either of these two chains via genetic defects.

β-Thalassemia major is characterized by a defect in both β-globin genes. These patients have a severe phenotype and 80% die within the first 5 years of life. They require the close care of a hematologist with frequent transfusions or splenectomy. Patients with β-thalassemia minor are heterozygous for the β-globin gene defect and therefore have varying concentrations of abnormal β-globin. Many times patients with β-thalassemia minor are clinically asymptomatic and rarely require treatment. These patients may require transfusions after vaginal delivery or surgery.

Four genes code for the α-globin subunits; therefore, the degree of severity depends on the number of genes affected. Hydrops fetalis results when all four copies of the α-globin genes are damaged. The lack of α-globin subunits causes fetal γ-globin subunits to aggregate resulting in tissue anoxia and intrauterine fetal death. This form is referred to as hemoglobin Bart's disease. Hemoglobin H disease results when three α-globin genes are defective. The diminished amount of α-globin results in aggregates of β-globins, called hemoglobin H. Hemoglobin H has a disproportionately high affinity for oxygen, thus delivering less oxygen to peripheral tissues. There are severe clinical consequences such as chronic hemolysis, frequent hospitalizations, and decreased life span. Care of these patients is similar to that of β-thalassemia major patients.

α-Thalassemia minor has two of the four α-globin genes affected, resulting in clinically minimal symptoms that do not require treatment. Again, they may require transfusion after blood loss.

The silent carrier state is present when a single α-globin gene is deleted. A patient with this condition may not know and would not require treatment. This is also called α-thalassemia minima.

In general, transfusions are used for severe microcytic anemia caused by thalassemia. Chronic blood transfusions leave a patient susceptible to iron overload. Iron chelation therapy is classically done with deferoxamine. Deferoxamine is given IM 0.5 to 1 mg daily. However, deferasirox (Exjade) can also be used and is questionably tolerated better by patients. Splenectomy and allogenic bone marrow transplantation should be considered in severe thalassemia cases.

All patients with thalassemia should be offered genetic counseling prior to family planning.

NORMOCYTIC ANEMIA

Normocytic anemias consist of a very widespread group of anemias that can be grouped into two basic categories: hemolytic or nonhemolytic. Normocytic anemias are those with an MCV that is within the normal range of 80 to 100 fL. In this section hemolysis and blood loss are discussed.

ACUTE BLOOD LOSS

The investigation of chronic blood loss can be found in the discussion of iron deficiency anemia within this chapter. In this section we focus on acute losses only.

Symptoms

- Relate to the amount of blood lost (>2 L is severe)
- Shortness of breath at rest or with exertion
- Restlessness
- Anxiety
- Syncope with change in position
- Confusion

Signs

- Vasovagal reaction
- Orthostatic hypotension
- Hypotension
- Tachycardia
- Shock

Workup

- Following a trauma it is usually customary to rule out massive bleeding with inspection and rapid scans. In the nontrauma

setting, ruling out bleeding is not always at the forefront. If the bleed is external, it is usually obvious that the patient is bleeding. If the bleeding is internal, it is not always that obvious. Close observation of vital signs and mental status are thus important when caring for a patient. Patients can bleed into their GI tract, abdomen, chest, or retroperitoneum from GI tract varices, broken bones, ruptured vessels or organs, or cancers. Sometimes large volumes of blood can acquire before any symptoms develop. Usually this volume is around 1 L or 20% of total blood volume. The first sign is usually tachycardia, which usually occurs prior to hypotension. Initial resuscitation generally proceeds with IV fluids; however, in trauma fluid resuscitation prior to definitive care may negatively effect outcome in some circumstances. The anemia is usually then only discovered after attempts at volume replacement to combat the hypotension.

- Screening for a bleed in the GI tract can be done via stool Hemoccult test or gastric lavage and Gastroccult for upper GI bleeds. Exact localization of the bleed may require either an esophagogastroduodenoscopy (EGD) and/or a colonoscopy. Bleeds in the GI tract not able to be seen with either of these two modalities may require a tagged red blood cell scan.

Comments and Treatment Considerations

Treatment of the cause of the bleed is critical. The endpoint for transfusions depends on patient status and comorbidities. If the anemia is not severe, no specific therapy is required because the body will compensate for the loss. The patient must have functioning kidneys in order to make erythropoietin, and functioning bone marrow for this to take place. Adequate iron is also required. Reticulocytosis will be noticed within days.

Each unit of packed RBCs raises the hematocrit by about 4%.

There are 300 mL in 1 unit of packed RBCs and 200 of them are RBCs.

Signs of major transfusion reactions are fever, chills, backache, and headache. If severe there may be dyspnea, hypotension, and vascular collapse. Stop the transfusion! Disseminated intravascular coagulation (DIC) and renal failure can occur. The patient will need aggressive hydration.

If the patient develops fever and chills within 12 hours of transfusion, it is a reaction to antigens on the white cells still present in the blood given. These reactions are usually not severe and can be treated with acetaminophen and diphenhydramine. Often patients are pretreated with these agents. If a patient requires frequent transfusions, leukopoor blood can be ordered. This blood has the white cells totally washed out.

The risk of hepatitis B virus (HBV) infection from a transfusion is 1:200,000 per unit, and of human immunodeficiency virus (HIV) 1:250,000 per unit. The most common infection risk is hepatitis C virus (HCV), with a risk of 1:3300 per unit.

HEMOLYSIS

There is a wide variety of causes of hemolytic anemias, which can be characterized as intrinsic red cell defects or extrinsic red cell defects. Intrinsic red cell defect implies that there is something wrong with the red cell itself that causes it to be destroyed. Extrinsic red cell defects include things that happen outside the red cell that bring attention to the red cell, which in turn causes it to be destroyed. Extrinsic defects also include various environmental hazards red cells wander through that may end up terminating their life. Refer to Table 4-5 for a classification of hemolytic anemias.

Symptoms

- Fatigue
- Red-brown urine
- Acute pain episodes (sickle cell disease [SCD])
- Vary widely depending on the disease

Signs

- Jaundice
- Splenomegaly
- Chronic leg ulcers (hereditary spherocytosis [HS], SCD)
- Vary widely depending on the disease

Workup

- A careful history and physical examination are essential, particularly regarding medications and possible toxin exposures. Many of the anemias in this category are inherited.
- Due to the survival time of RBCs (120 days), one can expect a fall in hematocrit of up to 3% per week if the bone marrow is dysfunctional. If it declines at a faster rate, blood loss or hemolysis are to blame.
- The laboratory workup will reveal reticulocytosis as a key feature in the diagnosis of hemolysis. The exceptions to this rule are (1) reticulocytosis *does not* occur with hemolysis in the setting of a second disorder such as infection, or folate deficiency, and (2) reticulocytosis *does* occur during recovery from other nonhemolytic anemias such as B_{12} or folate deficiencies and from an acute bleed. Another laboratory value that is shared among all hemolytic anemias is serum haptoglobin level. Haptoglobin is a binding protein for hemoglobin, so its levels decrease during hemolysis. Haptoglobin is not a reliable indicator alone. Urine can be examined for hemoglobin and hemosiderin if the hemolysis is intravascular. Hemoglobin and methemoglobin can also be measured in serum with severe intravascular hemolysis. Increased total and indirect bilirubin are also indicators of hemolysis because they are stored inside red cells. Total bilirubin may rise above 4 mg/dL; suspect liver dysfunction if higher. Finally, LDH levels should be included. The microangiopathic anemias will elevate LDH.

Table 4-5. Classification of Hemolytic Anemias

INTRINSIC RBC DEFECTS	EXTRINSIC RBC DEFECTS
MEMBRANE DEFECTS: • Hereditary spherocytosis • Hereditary elliptocytosis • Paroxysmal nocturnal hemoglobinuria	AUTOIMMUNE Warm antibody mediated • CLL • SLE • Idiopathic Cold antibody mediated • *Mycoplasma* • Idiopathic
ENZYME DEFICIENCIES: • Pyruvate kinase deficiency • G6PD deficiency • Methemoglobinemia • Severe hypophosphatemia	LOCAL ENVIRONMENT Microangiopathic • TTP/HUS • DIC • Valve hemolysis • Metastatic adenocarcinoma • Vasculitis Hypersplenism Burns
HEMOGLOBINOPATHIES: • Sickle cell syndromes • Unstable hemoglobins • Methemoglobinemia	RBC INFECTIONS • Malaria • *Clostridium* • *Borrelia* OTHER • Drug-induced (e.g., PCN)

CLL, Chronic lymphocytic leukemia; *DIC,* disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate dehydrogenase; *HUS,* hemolytic-uremic syndrome; *PCN,* penicillin; *RBC,* red blood cell; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

- Peripheral blood smear is useful (i.e., sickled cells). RBC membrane defects are readily diagnosed here. Enzyme deficiencies can also be diagnosed via this method combined with specific enzyme assays and DNA sequencing. Hemoglobinopathies require the use of hemoglobin electophoresis in addition to peripheral smear.
- Immune-mediated hemolysis is diagnosed with the Coombs' antiglobulin test. The direct Coombs' test assays whether there are immunoglobulins or complement components attached to red cells. If immunoglobulins are present on the red cells, they will clump together when the Coombs' reagent is added. If this happens at body temperature, the patient has a "warm" antibody-mediated hemolytic anemia. If it has to be cooled to clump, then the patient has a "cold" antibody-mediated hemolytic anemia. The indirect Coombs' test may also be needed to diagnose the immune-mediated anemias. Serum complement levels, specifically C3 and C4, may be depressed during immune-mediated hemolysis.

- When RBCs are destroyed due to mechanical trauma they encounter in their environment they are fragmented and this can be seen on peripheral smear (schistocytes). The other clinical symptoms and objective signs of the microangiopathic hemolytic anemias are used to key into their diagnosis. One important form of mechanical hemolysis that may be encountered in the primary caregiver's office is runner's anemia. This is when hemolysis occurs from the repetitive pounding of the feet on the pavement during frequent running. This causes hemolysis and anemia that is easily diagnosed with a little time off from running and rechecking the CBC.
- Splenomegaly can be diagnosed by physical examination versus simple imaging.
- Diagnosing infection-induced hemolysis requires looking at the red cell for characteristic signs of infection such as those associated with *Plasmodium falciparum*. Serologic markers are used for specific infections.

Comments and Treatment Considerations

It is important to give patients with hemolytic anemia folic acid supplementation to keep up with the demand of reticulocytosis.

Following splenectomy, patients are at risk for infection with encapsulated bacteria, so immunize against *Pneumococcus* and *Meningococcus*.

Cholecystectomy is an option for bilirubin gallstone-induced cholecystitis.

Specific treatment depends on the type of hemolysis. The common forms are discussed here.

Hereditary spherocytosis is inherited in an autosomal dominant pattern. Diagnosis is via peripheral smear and the osmotic fragility test. The MCHC will be elevated on the CBC. The severity of the disease determines treatment; splenectomy is the definitive treatment. Blood transfusions are given as needed.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is transmitted in an X-linked pattern. Oxidative stress causes hemolysis and occurs when patients are exposed to things such as fava beans, sulfa drugs, moth balls, or primaquine. Infections can also incite acute events. The flares are sporadic and can be prevented with avoidance of culprit substances. During acute events patients may need hospitalization, transfusions, and hydration.

Sickle cell anemia is an autosomal recessive disease and is diagnosed via hemoglobin electrophoresis. A wide spectrum of disease exists from asymptomatic to severe. Patients that are homozygous for the disease are discovered during childhood. When attacks occur, red cells sickle and become clogged in the microvasculature. The most common presentation is the acute pain crisis with pain anywhere in the body. These episodes are treated with hydration, oxygenation, adequate pain control, transfusions as needed, and attention to any underlying infection or stress that may have precipitated the attack. Hydroxyurea may reduce sickling and is given prophylactically. “Acute chest syndrome” is the triad of chest pain, pulmonary infiltrate, and fever. This can represent pneumonia or

pulmonary infarct, or sometimes both. Prompt attention is required. These patients usually autoinfarct their spleen early in life, so it is as if they have had a splenectomy. Children are given prophylactic penicillin until age 5.

Autoimmune hemolytic anemia is often treated with corticosteroids, especially the warm antibody-mediated type. Other options for long-term treatment include azathioprine, cyclosporine, and rituximab. Intravenous immune globulin (IVIg) can be used in the acute setting only for adults. Exchange transfusions are also an option. Splenectomy is used for refractory cases.

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